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# The Use of Ortho-chelating Arenethiolate Non-transferable Groups in the Copper(I) Catalyzed Selective α or γ Substitution of Acyclic Allylic Substrates with Grignard Reagents.

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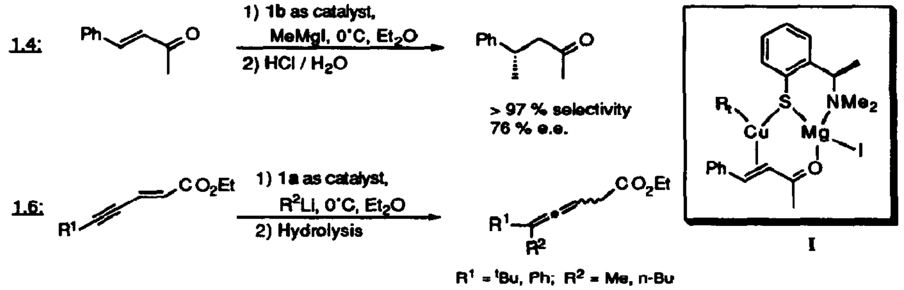
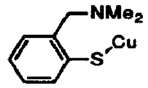
***Abstract:*** Ortho-amino arenethiolatocopper(I) compounds are excellent catalysts for the cross-coupling reaction of Grignard reagents with acyclic allylic substrates. For example, reaction of *n*-BuMgI with geranyl acetate in $Et_2O$ at 0 °C yields quantitatively the γ substitution product, whereas the same reaction in THF at -30 °C affords selectively the α substitution product.

The copper-catalyzed cross-coupling reaction of allylic substrates has attracted much interest during recent years.[1,2] A key-feature of this reaction is the regioselectivity with respect to nucleophilic displacement; the leaving group can be displaced either on the α ($S_N2$) or γ ($S_N2'$) position by the organometallic reagent.[2] In the reactions of allylic substrates with Grignard reagents, various copper(I) salts (*e.g.* CuCl, CuCN and $Li_2CuCl_4$) have been used in stoichiometric as well as catalytic amounts.[1,2] Recently, van Koten *et al.* showed that copper(I) arenethiolates[3] with a tertiary amino substituent (CuSAr, **1a-d**) can be used in catalytic amounts with excellent chemo- and regioselectivities in 1,4-addition[4] and 1,6-addition[5] reactions of Grignard and lithium reagents to acylic enones; with a chiral Cu(I) arenethiolate (**1b**) enantioselectivities of up to 76% were obtained in 1,4-addition reactions (Scheme 1).[4d] Recently Pfaltz *et al.*, using chiral oxazoline arenethiolates, achieved e.e.'s of 83-87% in 1,4-addition reactions with cyclic enones.[6]

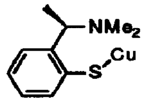
*Scheme 1*



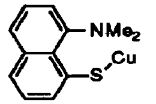
These results indicate that the *ortho*-amino arenethiolate anion ($ArS^-$) has excellent properties as a non-transferable group in 1,4- and 1,6-addition reactions. Separate studies of the heterocuprates formed in reaction mixtures containing the CuSAr catalyst and an organometallic reagent (CuR, LiR, or RMgX) have indicated a structure for the kinetic CuSAr/RMgX/enone intermediate in these conjugate addition reactions which is represented by **I** in Scheme 1.[3,4,7] In anticipation that combined bonding of both the alkene function to Cu and a second donor function to Mg is important for the activation and transformation of these substrates, we have now studied the applicability of CuSAr catalysts in cross-coupling reactions of Grignard reagents with acyclic allylic acetates.



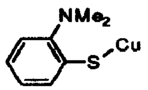
**1a** (trimer)



**1b** (trimer)



**1c** (nonamer)



**1d** (trimer)

Two allylic acetates, *i.e.* geranyl acetate (**2**) and (*E*)-1-acetoxy-4-phenoxy-2-butene (**5**), have been reacted with 1.25 equiv. of *n*-BuMgI in the presence of CuSAr (**1a-d**) as catalyst. The influence of the following parameters in this reaction with **2** has been studied in detail: (**i**) the concentration of CuSAr, (**ii**) the type of solvent, (**iii**) the addition rate of the Grignard reagent, and (**iv**) the type of copper(I) catalyst. The results are given in Table 1.

(**i**) Concentration of Arenethiolatocopper(I) Catalyst: Independent of the catalytic amount of **1a** in the range 4.5-15 mol% (based on monomeric copper units) complete conversion of **2** as well as complete $\gamma$ selectivity is obtained in $Et_2O$ at 0 °C with 120 minutes addition time (entry 1). Without **1a** under exactly the same reaction conditions a conversion of 34% is obtained with an $\alpha : \gamma$ ratio of 71 : 29 (entry 3).

(**ii**) The Type of Solvent: In the cross-coupling reaction with **2** the regioselectivity can be tuned from highly selective $\gamma$ substitution in $Et_2O$ at 0 °C (entry 1) to complete $\alpha$ substitution in THF at -30 °C when using 15 mol% of **1a** (entry 5). Even in THF at 0 °C an $\alpha : \gamma$ ratio of 86 : 14 is obtained (entry 4). This dramatic solvent effect (*cf.* entries 1, 4 and 5) on changing from $Et_2O$ to THF was previously observed in CuCN-catalyzed Grignard couplings with allylic acetates.[2a,8]

(**iii**) Addition Rate of the Grignard Reagent: Addition of *n*-BuMgI in 5 minutes to a solution of **1a** (15 mol%) and **2** in $Et_2O$ results in a 8 : 92 ($\alpha : \gamma$) product distribution (entry 2), while slow addition of *n*-BuMgI in 120 minutes affords only the $\gamma$ substitution product (entry 1). These results show that the $\gamma$ selectivity increases with the addition time[2a] although the effect is less accentuated in $Et_2O$ where $\gamma$ substitution predominates even with fast addition.

(**iv**) Type of Copper(I) Catalyst: Since the non-transferable amino arenethiolate anions in the four CuSAr catalysts, **1a-d**, differ with respect to the donor abilities of their N,S-binding sites as well as in the flexibility of the hydrocarbon chain connecting the N- and S-donor atoms, these anions should have a distinct influence on the selectivity of the substitution reaction. In the cross-coupling reaction with **2**, the catalysts **1b** and **1c** afford the same high selectivity for $\gamma$ substitution as **1a** (entries 6 and 7), whereas complex **1d** gives a much lower $\alpha : \gamma$ ratio of 28 : 72 (entry 8). Moreover with **1d** the chemoselectivity is lower and 25% of geraniol is also formed. It is noteworthy that the use of pure CuSPh (entry 9) or *in situ* prepared CuSPh•LiI (entry 10), affords a similar lower regioselectivity, *i.e.* $\alpha : \gamma$ ratio of 21 : 79. These results strongly indicate that the $2\text{-}Me_2NC_6H_4S$ anion in **1d** retains its non-transferable properties, but that the N,S chelation is not as effective as in the other catalysts, most probably as a result of a too rigid N,S orientation as well as a too small MSCCN chelate ring size. The high reactivity (100% conversion) and selectivity (98-100% γ) of the CuSAr catalysts **1a**-**c** in $Et_2O$ is very striking (entries 1, 6 and 7) particularly when one compares the use of $Li_2CuCl_4$[2a] which affords exclusively the α substitution product (>99% selectivity) in 86% conversion (entry 11).

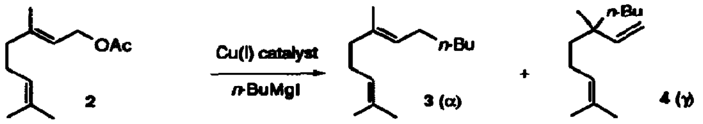


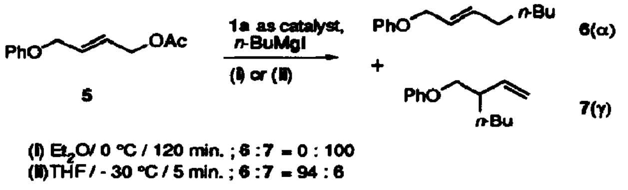
Table 1. The cross-coupling reaction of *n*-BuMgI with **2** using various copper(I) catalysts.[a]

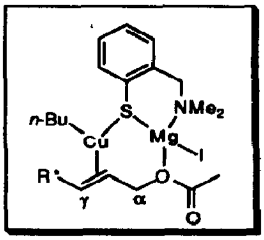
| Entry | Catalyst | Solvent | Temp. (°C) | Addition time (min.) | Conversion[b] of **2** (%) | Yield[b] (**3** + **4**) (%) | α : γ ratio[b] (**3** : **4**) (%) |
|---|---|---|---|---|---|---|---|
| 1. | **1a** | $Et_2O$ | 0 | 120 | 100 | 100 | 0 : 100 |
| 2. | **1a** | $Et_2O$ | 0 | 5 | 93 | 93 | 8 : 92 |
| 3. | - | $Et_2O$ | 0 | 120 | 34 | 17[c] | 71 : 29 |
| 4. | **1a** | THF | 0 | 120 | 100 | 100 | 86 : 14 |
| 5. | **1a** | THF | -30 | 5 | 100 | 100 | 100 : 0 |
| 6. | **1b** | $Et_2O$ | 0 | 120 | 100 | 100 | 0 : 100 |
| 7. | **1c** | $Et_2O$ | 0 | 120 | 100 | 100 | 2 : 98 |
| 8. | **1d** | $Et_2O$ | 0 | 120 | 100 | 75[c] | 28 : 72 |
| 9. | PhSCu | $Et_2O$ | 0 | 120 | 96 | 60 | 21 : 79 |
| 10. | PhSCu•LiI | $Et_2O$ | 0 | 120 | 98 | 98 | 20 : 80 |
| 11. | $Li_2CuCl_4$ | $Et_2O$ | 0 | 120 | 86 | 86 | >99 : <1 |

a) A solution of **1** (0.15 mmol) in toluene (15 mL) was added to a solution of the allylic substrate (1.0 mmol) in diethyl ether (15 mL). To this mixture was added dropwise the Grignard reagent (1.25 mmol) dissolved in diethyl ether (100 mL). After complete addition the reaction mixture wa sthen stirred for 30-60 minutes. b) Determined by capillary GC using *n*-undecane as internal standard. c) The only other product is geraniol.

Two experiments using substrate **5** have also been carried out. Addition of *n*-BuMgI (1.25 equiv.) within 120 minutes to a mixture of **5** (1 equiv.) and 9 mol% of **1a** (based on monomeric copper units) in $Et_2O$ at 0 °C affords the corresponding γ substitution product **7** quantitatively (Scheme 2). When the same reaction is carried out in THF at -30 °C with an addition time of 5 minutes the α substitution product **6** is selectively formed (α : γ = 94 : 6).

*Scheme 2*





II

In a weakly coordinating solvent, *e.g.* $Et_2O$, our results for the high regio- and chemoselectivity of reactions with **2** and **5** as substrates can be explained by formation of II[4e] as a key-intermediate, *i.e.* the allylic acetate anchors to the Cu-Mg arenethiolate unit in a bidentate fashion via coordination of the double bond to copper[7] and coordination of the oxygen to magnesium. In this way the *n*-Bu group is directed to the γ-position via a σ-allyl($C_\gamma$) copper species.[2] The corresponding intermediate anticipated in a strongly coordinating solvent, *e.g.* THF, has little possibility for Mg-O coordination due to Mg-THF interaction. In THF this kinetic intermediate would rearrange via a σ-allyl($C_\gamma$)/π-allyl/σ-allyl($C_\alpha$) sequence[2] resulting in a product with exclusive α substitution.

The results of this report show the excellent applicability of these (readily soluble) CuSAr catalysts in cross-coupling reactions. The most important conclusion is that, depending on the reaction conditions, these catalyzed substitutions can be carried out with complete regioselectivity (either α or γ) with the choice of solvent being one of the most critical factors. Research is now in progress to explore the scope of these reactions with other Grignard reagents and other (cyclic) allylic substrates as well as to investigate the use of chiral CuSAr* catalysts for enantioselective addition and substitution reactions (see entry 6).

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